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Recommendations for Future Research on National Ambient Air Quality Standards for Ozone and Lead

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Report Of The Clean Air Scientific Advisory Committee (CASAC)

Recommendations For Future Research On National Ambient Air Quality Standards For Ozone And Lead

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D C 20460

September 30, 1987

OFFICE OF
THE ADMINISTRATOR

The Honorable Lee M. Thomas
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Dear Mr. Thomas:

The Clean Air Scientific Advisory Committee (CASAC) has completed its assessment of research needed to support the development of National Ambient Air Quality Standards (NAAQS) for Ozone and for Lead. This report, along with the December 30, 1983 report which outlined research needs for carbon monoxide, nitrogen oxides, particulate matter, and sulfur oxides, is in response to the mandate under the Clean Air Act Amendments of 1977 to provide you with advice concerning research needs for ambient pollutants.

Within each of the major research areas identified for ozone and for lead, we summarize the need for the research and assign priorities. These priorities represent a continuum since we believe that all of the research needs that we have identified are of importance to the Agency. For ozone, we have identified research needs in atmospheric chemistry, health effects, and agriculture, forests and related ecosystems; for lead, we have identified research needs in atmospheric processes, exposure, metabolism, and biological and health effects. We have also provided recommendations on the design of the National Health and Nutrition Evaluation Survey (NHANES III). Clearly, each research program must be structured so that those studies which can determine the importance of critical variables and mechanisms are started early and pursued vigorously. This places additional responsibility on the Agency's research staff to ensure that timely and appropriate research resource allocations are made. It is worth emphasizing that the planning of future studies should be integrated with the findings from ongoing research.

The research program which the Committee recommends for ozone can be pursued and completed within the next five years at a cost which, while relatively large in relation to the current EPA budget for criteria pollutant research is relatively modest in relation to the costs of current monitoring and control efforts. The research results are almost certain to provide a much better scientific basis for the ozone NAAQS promulgation in the mid 1990s than that available today.

Thank you for the opportunity to present our views on these important human health and welfare issues. We request that the Agency officially respond to the scientific advice contained in the attached report.

Sincerely,

Morton Lippmann

Morton Lippmann
Chairman
Clean Air Scientific
Advisory Committee

cc: A. James Barnes
Vaun Newill
Craig Potter
Terry Yosie

U.S. ENVIRONMENTAL PROTECTION AGENCY

NOTICE

This report has been written as a part of the activities of the Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide a balanced expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency, and hence the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute endorsement of recommendation for use.

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May 1987

U.S. Environmental Protection Agency
Science Advisory Board
Clean Air Scientific Advisory Committee

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Dr. Morton Lippmann, Professor, Institute of Environmental Medicine, NYU Medical Center, Tuxedo, New York 10987

Members

Dr. James D. Crapo, Associate Professor of Medicine, Chief, Division of Allergy, Critical Care and Respiratory Medicine, Box 3177, Duke University Medical Center, Durham, North Carolina 27710

Dr. Robert Frank, Professor of Environmental Health Sciences, Johns Hopkins School of Hygiene and Public Health, 615 N. Wolfe Street, Baltimore, Maryland 21205

Dr. Paul B. Hammond, Professor of Environmental Health, University of Cincinnati College of Medicine, Kettering Laboratory, 3223 Eden Avenue, Cincinnati, Ohio 45267-0056

Dr. Jay S. Jacobson, Plant Physiologist, Boyce Thompson Institute, Tower Road, Ithaca, New York 14853

Dr. Jane Q. Koenig, Research Associate Professor, Department of Environmental Health, SC-34, University of Washington, Seattle, Washington 98195

Dr. Timothy Larson, Environmental Engineering and Science Program, Department of Civil Engineering, FX-10, University of Washington, Seattle, Washington 98195

Dr. D. Warner North, Principal, Decision Focus Inc., Los Altos Office Center, Suite 200, 4984 El Camino Real, Los Altos, California 94022

Dr. Gilbert S. Omenn, Professor and Dean, School of Public Health and Community Medicine, SC-30, University of Washington, Seattle, Washington 98195

Dr. Michael B. Rabinowitz, Harvard Medical School, c/o Marine Biological Laboratory, Woods Hole, Massachusetts 02543

Dr. Robert D. Rowe, Vice President, Environmental and Resource Economics, Energy and Resource Consultants, Inc., 207 Canyon Boulevard, Boulder, Colorado 80302

Dr. Ellen K. Silbergeld, Senior Scientist, Environmental Defense Fund, 1616 P. Street, N.W., Washington, D.C. 20036

Dr. Mark J. Utell, Co-Director, Pulmonary Disease Unit, Associate Professor of Medicine and Toxicology in Radiation Biology and Biophysics, University of Rochester Medical Center, Box 692, Rochester, New York 14642

Dr. James H. Ware, Associate Professor, Harvard School of Public Health, Department of Biostatistics, 677 Huntington Avenue, Boston, Massachusetts 02115

Dr. George T. Wolff, Senior Staff Research Scientist, General Motors Research Labs, Environmental Science Department, Warren, Michigan 48090

Executive Secretary

Mr. A. Robert Flaak, U.S. Environmental Protection Agency, Science Advisory Board (A-101F), Washington, D.C. 20460

September 1987

U.S. Environmental Protection Agency
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Clean Air Scientific Advisory Committee

Chairman

Dr. Morton Lippmann, Professor, Institute of Environmental Medicine, NYU Medical Center, Tuxedo, New York 10987

Members

Dr. Robert Frank, Professor of Environmental Health Sciences, Johns Hopkins School of Hygiene and Public Health, 615 N. Wolfe Street, Baltimore, Maryland 21205

Dr. Warren B. Johnson, Manager, Research Aviation Facility, National Center for Atmospheric Research, P.O. Box 3000, Boulder, Colorado 80307

Dr. Timothy Larson, Research Associate, Environmental Engineering and Science Program, Department of Civil Engineering FX-10, University of Washington, Seattle, Washington 98195

Dr. Gilbert S. Omenn, Professor and Dean, School of Public Health and Community Medicine, SC-30, University of Washington, Seattle, Washington 98195

Dr. James H. Ware, Associate Professor, Harvard School of Public Health, Department of Biostatistics, 677 Huntington Avenue, Boston, Massachusetts 02115

Dr. Jerry Wesolowski, Chief, Air and Industrial Hygiene Laboratory, California Department of Health, 2151 Berkeley Way, Berkeley, California 94704

Executive Secretary

Mr. A. Robert Flaak, U.S. Environmental Protection Agency, Science Advisory Board (A-101F), Washington, D.C. 20460

1. EXECUTIVE SUMMARY

This is the second in a series of reports prepared by the Clean Air Scientific Advisory Committee (CASAC) providing recommendations to the U.S. Environmental Protection Agency on research needed to develop and support National Ambient Air Quality Standards (NAAQS). The first report, issued in December 1983, provided research recommendations on four of the six criteria pollutants: carbon monoxide, nitrogen oxides, particulate matter, and sulfur oxides. This present report provides research recommendations for the two remaining criteria pollutants: ozone and lead.

The research recommendations for ozone are presented in three parts: 1) atmospheric chemistry; 2) health effects; and 3) agriculture, forests and related ecosystems. Each part is critical to setting an ozone NAAQS. The latter two areas are critical in establishing exposure-response relationships for the effects that ambient ozone produces. However, without a better understanding of exposure profiles, scientists and regulators cannot accurately establish the extent of the effects of ambient ozone exposure on public health and welfare. Furthermore, without a better understanding of atmospheric chemistry, we cannot predict either the frequency of excessive exposures or the influence of the various sources of the ozone precursors on the ambient concentrations.

The Committee has the following high priority research recommendations for ozone:

Atmospheric Chemistry

- The Committee proposes two research programs which will help develop urban-scale and regional-scale models that can be used for regulatory purposes, and which will determine existing and future ozone trends to assess the impact of precursor emissions.

Health Effects

- Research which emphasizes the identification of ozone health effects related to chronic low-level exposures.
- Population studies linking long-term ozone exposure with development of chronic respiratory system damage.
- Quantitative animal-to-human extrapolation.
- Interactions of ozone with other air pollutants.
- Influence of ozone on host defenses against infections and neoplastic diseases.
- Role of inflammation in response to ozone.

Agriculture, Forests, and Related Ecosystems

- Additional exposure statistics research.
- General physiological/biological process models for crops and trees.
- Comparisons of ozone flux in chambers to crop canopies.
- Ozone dose-response of major tree species and overall forest productivity analyses.

The research recommendations for lead are presented in four parts: 1) atmospheric processes; 2) exposure considerations; 3) lead metabolism; and 4) biological and health effects. In addition, the Committee has provided recommendations on the design of the forthcoming National Health and Nutrition Evaluation Survey (NHANES III).

Atmospheric Processes

- Reassessment of the relative impact of point sources and gasoline on ambient air lead.
- Assessment of the impact of air lead on lead in other media to which man is exposed (i.e., food and water).
- Assessment of factors which determine the transfer of lead from dump sites to air and water.

Exposure Considerations

- Importance of soil and dust ingestion in children as sources of lead.
- Bioavailability of lead as a function of particle size and chemical form.
- Contribution of foods to total lead intake, including processing and packaging.
- Contribution of drinking water to total lead intake, including water used in food and beverage preparation.

Lead Metabolism

- Development of better indices of lead exposure.
- Biokinetic modeling with special emphasis on the fetus and placenta, as well as bone in both pregnant women and in the elderly.
- Dietary factors influencing lead absorption.

Biological and Health Effects

- Continued, uninterrupted support for current prospective studies of neurobehavioral effects of lead in children to school age and beyond.

In connection with the forthcoming NHANES III study, the Committee urges EPA to consider questionnaire items to aid in establishing if a subject's blood lead concentration is representative of long-term duration of exposure or if it reflects a recent significant incident, and secondly, to use the best possible methodology for blood lead determinations.

II. INTRODUCTION

A major responsibility of the Clean Air Scientific Advisory Committee (CASAC), as established in the Clean Air Amendments of 1977, is to provide scientific advice on additional knowledge that is required for evaluating existing, or setting new or revised National Ambient Air Quality Standards (NAAQS). On December 30, 1983, the CASAC issued the first of an eventual series of reviews intended to evaluate the state of research knowledge and needs for criteria air pollutants. This first report assessed five generic research needs for such pollutants that included: 1) development of a program in air pollution epidemiology; 2) development of a program in extrapolation modeling; 3) research relating concentrations at monitoring sites to human exposures; 4) research relating exposures to dose; and 5) responses to multiple pollutant exposures. In addition, the CASAC identified research directions and needs for four specific pollutants for which it had reviewed air quality criteria documents: carbon monoxide, nitrogen oxides, particulate matter, and sulfur oxides.

The Committee met on May 21-22, 1987 and July 15, 1987 to discuss and identify research directions and needs for ozone and for lead. In this present report, the CASAC has reviewed the research recommendations for ambient ozone and lead prepared by EPA staff, members of the public, and its own members and consultants, and has prepared a set of research recommendations for each pollutant with a statement of priorities for the next five years. The priorities are based upon the need to address scientific issues having the greatest potential impact on setting a NAAQS to protect the public health and welfare.

Research recommendations are identified as first, second, and third priorities. It should be noted that the Committee believes that all the recommendations presented are of great concern to the Agency. The three priorities should be viewed as a continuum. While the recommendations and priorities are those of CASAC, we gratefully acknowledge the excellent preliminary work by EPA staff, and contributions from members of the public.

III. RESEARCH NEEDED FOR FUTURE DECISIONS ON NATIONAL AMBIENT AIR QUALITY STANDARDS FOR OZONE

A. Introduction

While research performed since the last ozone NAAQS promulgation in 1979 has greatly increased our knowledge of ozone formation and persistence in the troposphere, its effects on public welfare, and its effects on human health, major knowledge gaps and areas of uncertainty remain. These gaps and uncertainties limit the ability of the Administrator to identify the effects which result from various combinations of concentration, exposure time, and ventilation rate, and the degree to which some pollutant associated effects are attributable to ozone alone, or to ozone in combination with other airborne pollutants. Thus, while much is known about ozone exposures and their effects, our current knowledge of effects remains incomplete, possibly leading to a promulgation of a standard which fails to protect against some adverse effects. On the other hand, the use of an overly conservative margin of safety to compensate for our incomplete understanding of the effects could lead to the promulgation of a standard which imposes very large burdens in society, in terms of unnecessary costs of control and/or restrictions on normal activities.

CASAC has approached the identification of research needs in a comprehensive manner, and it does not expect all of the needed research to be performed or funded by EPA. The Committee recognizes that some of the ozone research needs are being addressed by other sponsors of research in the public and private sectors, e.g. National Oceanic and Atmospheric Administration (NOAA) in atmospheric chemistry, U.S. Department of the Interior (USDOI) and U.S. Department of Agriculture (USDOA) in welfare effects, and the Health Effects Institute (HEI) in health related research. While CASAC understands the importance of these other research programs, it clearly sees EPA playing a lead role, and having the major responsibility for ensuring that all of the important scientific issues relevant to standard setting are addressed.

B. Atmospheric Chemistry

Because most of the major metropolitan areas in the United States still fail to meet the current National Ambient Air Quality Standard (NAAQS) for ozone, additional controls on emissions of volatile organic compounds (VOC) and, perhaps, nitrogen oxides (NO_x) may be required. All of the sources that were relatively easy to control are already subject to some degree of control. Thus, any additional controls will certainly be more expensive than previous ones, and they will have a significant economic impact on society. For these reasons, it is vital to know with reasonable certainty the impact that additional controls will have on ozone air quality. At present, scientists and regulators do not have that information because existing models have not been vali-

dated. It is also important to analyze emissions and air quality trends so to document the improvements in air quality resulting from emissions controls. At present, the documentation is inadequate.

In order to validate the models and document the trends, there is a need to develop an integrated, targeted research agenda for ozone. Two ultimate goals of these programs should include: 1) developing an urban-scale and a regional-scale model which can be used for regulatory and planning purposes, and 2) determining existing and future ozone trends to assess the impact of perturbations in precursor emissions. The CASAC proposes two research programs to achieve these goals, the elements of which are described below. In addition, a third program relating to a longer-term NAAQS for ozone is presented.

1. Modeling Program

a) Conduct sensitivity analyses using existing models to identify and improve critical model elements - Existing models have not been validated, and they can be improved. They can and should, however, be used to identify the types of ambient measurements needed for validation purposes and to determine which assumptions lead to the largest uncertainties. The models should be exercised to determine the sensitivity of the results to chemical mechanisms, boundary conditions, VOC speciation, VOC reactivity, aromatic chemistry, number of monitoring sites and locations, VOC/NO_x ratio, upwind and aloft concentrations of O_3, VOC, NO_x and carbonyls, grid size, meteorological parameters and other variables. Once the critical elements have been identified, programs to reduce the uncertainty of the model results due to uncertainties in the critical elements should be initiated. Such programs will undoubtedly include case (field studies), laboratory, and smog-chamber studies. In addition, there are several aspects of the models that are deficient and require further investigation. These include night time and heterogeneous chemistry, reactions involving and/or resulting in the production of aerosols, H_2O_2, HCOOH, PAN, and HNO_3, reactions involving natural hydrocarbons, cloud venting, deposition velocities as a function of time of day and surface, nocturnal jets, inability for the combined use of primitive-equation model and observations. Methods development for H_2O_2 should be a high priority because H_2O_2 data would help test various chemical mechanisms used in modeling. The models should be used to identify additional high priority species.

b) Develop ambient data bases for model testing and model validation - The first issue that needs to be addressed is the suitability of existing data bases generated from previous case studies. If there are any adequate data bases that exist, then testing should begin. Perhaps data bases generated from PEPE/NEROS or other studies are adequate. The regional-scale model, which incorporates long-range transport, should be applied in the Northeast while the urban-scale model should be applied in Los Angeles and another city in the Northeast. The Southern California Air Quality Study (SCAQS), conducted this summer (1987), was designed to generate a data base that can be used to test and validate models for ozone and particulate matter (PM-10). This data base is expected to be ready for use by 1990. Since there is such a long lead time required to plan and then validate the data from such studies, planning for additional field studies should begin as soon as possible.

c) Improve emission inventories - Present evidence suggests that the error level in the best available estimates of existing VOC and NO_x source strengths is nearly an order of magnitude larger than the magnitude of emissions reductions contemplated in current control strategies for O_3. Consequently, this is a critical element that needs improvement. Improved regional and urban-scale inventories for NO_x and speciated VOC are needed for the modeling and trend analyses, and an improved nation-wide inventory is need for the trend analysis. The overall emissions inventory should be examined first and uncertainties assigned to each category. Subsequent decisions can be made and priorities established based on which sources can achieve the greatest reduction in the overall VOC and NO_x emissions uncertainty. Some sources deserving priority attention include present in-use, on-road and off-road vehicles and equipment; diurnal, hot-soak and refueling emissions; small stationary sources; restaurants; and marine-related operations. Also, an accurate inventory of natural VOC emissions is needed because current estimates of the flux of natural VOC in the northeastern United States are at the same level as those from anthropogenic sources.

d) Run the validated models to determine optimum control strategies - The models should be exercised for a variety of urban areas to determine not only the degree of control required for attainment, but also the effect of nitrogen dioxide reductions on ozone concentrations. Depending on the local VOC/NO_x ratio, reducing NO_x could either increase or decrease ozone.

2. Trend Analyses Program

Even if models adequately represented real world phenomena, trend analyses are needed because they are the truer measure of progress. In addition, it is vital to know how much of the ozone problem is due to man's activities and how much is due to nature.

a) Establish and maintain ambient data bases - EPA needs to insure that the stations established for trend analysis are sited properly, and not relocated or terminated.

- Metropolitan ozone sites - The existing networks are probably sufficient.
- Rural ozone sites - A network of rural monitors needs to be established in both agricultural and remote areas. The remote sites should be in areas away from local sources so trends in the "background" ozone can be established.
- VOC and NO_x sites - Networks of VOC and NO_x monitors in metropolitan areas are needed. Many of the VOC and NO_x monitors need to be co-located so that the VOC/NO_x ratio, which is a critical input for any model, can be determined accurately. It is also important that the ratio be representative of the area as a whole. In addition, periodic measurements of individual VOC species at these sites are needed to determine the trends in VOC composition.

b) Trend analyses -- The following trends should be examined:

- Trends in the ambient concentrations of ozone, nitrogen dioxide, and volatile organic compounds by geographic area,
- Trends in the emissions of volatile organic compounds and nitrogen dioxide,
- Trends in ozone adjusted to eliminate the influence of meteorological variations.

c) Background Ozone - Because EPA is considering a long-term ozone standard that is approaching the natural background range of of 30 - 50 ppb, it is extremely important that this range be documented spatially and temporally, and that the sources of the background be quantified. For this effort, the following action should be taken:

- A network should be established to monitor the long-term trend in background ozone. The siting of these monitors is critical. It is important that they be upwind of the synoptic-scale region of interest to assess whether the regional ozone levels are elevated with respect to the upwind values.

- The relative magnitude of ozone from stratospheric intrusions and in-situ photochemical processes in the free troposphere needs to be determined. This will involve the monitoring of ozone and several stratospheric tracers, such as ^{7}beryllium and ^{90}strontium simultaneously, at different altitudes in the stratosphere and in the free troposphere, as well as on the surface. By examining the ratios of the tracers to each other and to ozone, and accounting for their natural decay and deposition processes, better estimates of these contributions can be made.

- The importance of natural hydrocarbons needs to be determined. This will involve improved emission estimates for not only the natural hydrocarbons but for the anthropogenic ones as well. In addition, laboratory experiments to obtain kinetic and mechanistic data for the major natural hydrocarbons are needed. These data would be used to develop improved reaction mechanisms which would be incorporated into photochemical models. The models would then be tested using appropriate smog chamber data. In addition, accurate ambient air measurements of all the hydrocarbons, natural as well as anthropogenic, will be required.

3. Predictive Air Quality Models for Long-Term Ozone Concentration Averaging Times

All the modeling efforts described above are designed to predict a one day, daytime hourly ozone profile, which could be used to generate an 8-hr or 7-hr mean if such a standard is implemented. However, there is also some thought being given to longer standards such as a 3-month mean of the daily 7-hr maximum values. At present, no models exist to address such a standard. When and if such a standard is implemented, models will be needed. Therefore, work should begin on the development of such a model if it appears that such a standard is likely.

C. Health Effects

The effects of ozone on human health have received intensive scientific scrutiny. Recent evidence has shown that inhalation of ozone at concentrations near ambient levels produces acute reversible changes in lung func-

tion. Yet significant gaps remain in the health effects data base for ozone: effects of low-level chronic exposure, relationships between acute and chronic effects, exposure-response relationships, and mechanisms of ozone-induced injury identify broad areas that are incompletely understood. The research program developed by the EPA has identified many of these major gaps and proposed realistic strategies for narrowing the remaining uncertainties. Given the wide array of research needs, and the limited resources available, the program has appropriately integrated controlled human clinical studies, animal toxicology, and/or epidemiology into its research planning.

The CASAC endorses the EPA efforts to advance ozone health research using a broad-based program including both human and animal studies. Although the CASAC is cognizant of the multiple approaches for subdividing the broad research categories, it chose to organize the long-range goals of the ozone research program into three general areas: a) chronic health effects, b) acute health effects, and c) mechanistic studies.

1. Chronic Health Effects

a) Objective

The objective of this research is to achieve an improved understanding of effects of chronic, low-level ozone exposure on the respiratory tract. At present, knowledge of acute effects following short-term ozone exposure is considerably greater than that following long-term, low-level inhalation. Several investigative approaches are identified:

- Chronic low-level animal exposures with endpoints including biochemical alterations, structural changes, alterations in pulmonary function, or other early indicators of ozone-induced lung disease.
- Population studies designed to determine whether long-term exposure is linked to development of chronic respiratory disease.
- Measurements of ozone dose and toxic effect in target tissues of several species to enhance the possibility of animal-to-man extrapolation.

b) Research Needs

The EPA should give very high priority to those components of its research program targeted at identifying ozone health effects related to chronic low-level exposures. Generally these efforts should take advantage of the findings from recently completely chronic exposure studies before developing new protocols.

First Priority Research Needs

- Effects of chronic ozone exposure. A major limitation of the ozone data-base relates to the limited understanding of chronic effects resulting from low-level exposure. The CASAC strongly supports studies involving long-term exposure of animals which are designed to elucidate the structural/functional implications of chronic diseases as determined by lung function, morphology, and biochemistry. Although efforts to develop early indicators of ozone-induced chronic lung disease are appropriate, it is not clear whether useful biomarkers would be developed for use in clinical epidemiologic studies of low-dose oxidant inhalation.

- The carefully designed epidemiologic study remains the ultimate mechanism for linking long-term ozone exposure with development of chronic respiratory system damage in humans. Despite the enthusiasm for such studies, the CASAC acknowledges their complexities. For example, the difficulties related to poor documentation of exposures, the variety of confounding variables, and uncertain endpoints have severely curtailed interpretation of such studies to date. Although the CASAC finds the possibility of using results from autopsies of accident victims interesting and imaginative, the problems of obtaining good tissue rapidly from autopsies, and difficulties in obtaining accurate exposure histories, somewhat dampened enthusiasm for this approach. Despite these reservations, the Committee encourages EPA to support and encourage studies of human populations in relation to chronic lung diseases associated with ozone exposure.

- Quantitative Animal-to-Man Extrapolation. This is an important research area that presents the opportunity to develop dosimetric models which allow adequate estimates of dose to specific target lung tissues across a variety of animal species. Emphasis should be placed on distinct species-specific as compared to across-species phenomena. Such an approach should enhance application of the toxicological data-base to risk assessment.

2. Acute Effects

a) Objective

The objective of this research area is to better understand the acute effects of ozone related to intermittent or prolonged daily exposures; in addition, it focuses on the potential connection between acute cellular damage to the respiratory tract and subsequent development of chronic disease.

b) **Research Needs**

EPA should continue to assign priority to the controlled clinical studies using the environmental chamber facility at Chapel Hill. The controlled clinical studies have been remarkably productive over the past five years in enhancing scientific understanding of acute ozone effects on healthy populations

First Priority Research Needs

- Health effects of prolonged daily exposures. The CASAC strongly endorses the concept of prolonged daily studies, with emphasis on the influence of concentration and duration of exposure. Such studies should prove instrumental in helping EPA decide whether a separate standard using a longer averaging time (for example, eight hours) is warranted for ozone.

- Determination of factors influencing the magnitude of the ozone response. One of the most interesting findings of the clinical ozone exposure study is the existance of wide variation in the magnitude of response in a healthy population. The CASAC supports further efforts to characterize the variability of response and to identify factors ranging from genes to cells that may influence this variability.

- Relationship between effects of acute and chronic ozone exposure. The Committee supports efforts to obtain a better understanding of the potential interaction between cellular and molecular events surrounding damge to the respiratory tissue from acute oxidant exposure and development of chronic pulmonary disease. The Committee recognizes the difficulty of undertaking such studies in the absence of valid markers of early injury or disease. However, it encourages *in vivo* studies at the biochemical and molecular level aimed at determining whether acute ozone exposed humans respond by producing factors capable of inducing inflammation, fibrosis, etc.

3. Mechanistic Studies

a) **Objective**

The objective of such studies is to further elucidate mechanisms reponsible for either acute or chronic ozone injury. This goal is broadly stated and applies to research recommendations that overlap between acute and chronic categories. EPA should continue to give very high priority to mechanistic research with ozone ranging from clinical physiological studies to the rapidly advancing arena of molecular biology.

b) Research Needs

First Priority Research Needs

- Interactions of ozone with other air pollutants. There is a need to investigate the potential for ozone to interact with other co-existing pollutants either in the air or in their effects after being taken up in the lungs. The real world ratios of pollutants are likely to be an influencing factor in provoking a potentiation of airway response. The few studies conducted in this area have not been highly rewarding, and this emphasizes the need for studying exposure-response curves rather than effects of single pollutant concentrations.

- Influence of ozone on host defenses against infectious and neoplastic diseases. Effects of ozone on viral infections are not well understood and studies of host-defense mechansims in both animals and humans are needed. There is also a need to better understand alterations in the immune system following both acute and chronic ozone exposure. In contrast, the CASAC has expressed less enthusiasm for studies designed to examine host defenses against "neoplastic disease". If the relationship between ozone exposure and neoplasia should be strengthened, then such studies would warrant a much higher priority.

- Role of inflammation in response to ozone. Inflammatory processes have been linked both to development of chronic lung disease as well as the acute development of airway hyperreactivity. The use of new clinical tools such as broncho-alveolar lavage in efforts to evaluate acute responses to ozone is a promising research opportunity. Inflammatory events may serve as a potential link between acute and chronic health effects resulting from ozone exposure. However, the Committee emphasizes the need for animal models to validate lavage findings and predictions of long-term effects.

Second Priority Research Needs

- Ozone molecular mechanisms of action. The Committee encourages studies aimed at elucidating the molecular mechanisms of ozone effects. However, it notes that while specific probes for studying molecular mechanisms are rapidly evolving, their current applications have yet to be demonstrated.

- Methodology development. There is a need for further method development, including physiological techniques to assess small airway function, monitoring of individual exposures, and statistical design and analysis. However, in some circumstances, such development would best be undertaken by other agencies with eventual application in EPA laboratories.

- Influence of ozone exposure on inhaled particle dosimetry. Alterations of dosimetry induced by ozone inhalation should prove useful in the extrapolation modeling process.

- Studies on the attenuation of ozone effects. Further evaluation of the biochemical, inflammatory, and morphologic changes associated with the well recognized phenomena of adaptation has merit. The influence of pharmocologic agents on the phenomena of ozone adaption warrants investigation.

- Responses of human bronchial and alveolar epithelium to ozone. Permeability of the pulmonary epithelial barrier is increased after ozone exposure. Further studies of changes in permeability from the nose to the alveolar level are encouraged in both laboratory animals and humans.

Third Priority Research Needs

- Identification of groups potentially at risk from ozone exposure. This is of obvious importance in protecting populations from ozone exposure but can best be investigated by studying factors influencing the magnitude of response.

- Genotoxic, carcinogenic, and co-carcinogenic effects of ozone. Although the influence of pollutant exposure on the development of cancer is of concern, it is not currently an area that warrants a higher priority because of the present lack of data on associations between ozone and cancer.

- Extrapulmonary effects. The Committee is not convinced that ozone studies targeted to effects beyond the respiratory tract should represent a major focus of the research program.

D. Agriculture, Forests, and Related Ecosystems

1. Agriculture

a) Objectives

The objective of research on the effects of ozone on agriculture is to improve the efficient evaluation of alternative secondary ozone ambient air quality standards. Broadly speaking, this requires:

- Accurate information as to the form of the standard that will best characterize the relationship between ozone and relevant measures of damage to crops and other important vegetation.

- Accurate and comprehensive information as to the physical, economic and social importance of ozone impacts on vegetation. What crops are affected; how much physical damage occurs; what is the economic and social importance of this damage and to whom, where, and when; and what is to be considered "adverse"?

- Provide generalizable understanding and modeling of the ozone-crop-welfare impacts' relationships that will provide the basis for updating the evaluation of the standard and stimulating methods to prevent and mitigate damage.

- Providing information in the most cost effective manner.

b) Research Needs

The National Crop Loss Assessment Network (NCLAN) has been an intensive, coordinated research effort sponsored by EPA and is now nearing completion. This program has developed a wealth of data. EPA should give first priority to a complete evaluation of the results of this research and related efforts supported by U.S. Department of Agriculture (USDA). The new information obtained and the remaining gaps in knowledge should be identified. Given the knowledge provided by NCLAN, EPA should identify the additional information needed to evaluate the current standard and support recommendations for modifications, where appropriate.

First Priority Research Needs

- Additional Exposure Statistics Work. In order to set efficient but not overly complicated standards, two lines of research are needed:

  (1) Examine alternative characterizations of exposure to ambient ozone and their effects upon crop yield. NCLAN focused upon 7-hour and 12-hour average exposures, but peak concentrations may be of more concern. Additional investigations should consider exposure characteristics in terms of duration, frequency, peak concentration, and maturity of plants.

  (2) Explore the relationship between patterns of ozone exposure and climate in different geographic regions and the response of vegetation. Different dose characteristics may best represent the scientific relationship between ambient ozone and crop yield for different regions, but they may be overly complex for standard setting. Therefore, generalized ozone dose-response relationships satisfactory for a range of environmental conditions should be developed for the most susceptible crop plants.

As a natural consequence of addressing alternative exposure measures in the dose-response relationship, the functional form of the relationship must be simultaneously addressed, although emphasis on this is in the second priority of research pursuits. This is because once general functional forms for the dose-response relationship are determined, refinements tend to have only a small impact on the physical and economic assessments.

- General physiological/biological process models. General process models are required concerning susceptibility and resistance to ozone. This provides explanations for dose-response relationships found and a basis for development of genetic lines of plants that can maintain satisfactory yield and quality at ambient levels of ozone, as it may be well into the next century before ambient levels decrease. This will reduce the need to repeat exposure studies for each new variety of crop.

- Accurate exposure data. Accurate monitoring information is needed on the concentrations of ozone and their variation with time in agricultural regions. Very limited ozone data is available for major agricultural regions. Often this data is the estimated growing season average based upon distant monitors. Improved data bases of multiple characteristics of exposure conditions throughout the growing season are needed to improve the application of dose response functions to better estimate yield losses and their resultant economic impacts on a more site specific basis.

- Flux comparisons. Compare flux of ozone to crop canopies in the field and in chambers used in the NCLAN program. The specific objective would be to determine whether fluxes in chambers, given the patterns and rates of air movements there, are similar or different than fluxes of ozone in the field, given the patterns and rates of air movements found in the regions where crops are grown. This effort would have to be undertaken for three seasons to encompass different climatic conditions and should be performed for those crops previously studied by NCLAN.

Second Priority Research Needs

- Additional dose-response studies on selected key high-valued crops in selected regions. The NCLAN program analyses are most applicable to major crops and growing conditions in the mid west and selected other locations. Additional dose-response analyses for the same crops in other regions and for key regional crops are needed to broaden the basis for evaluating the current secondary standard.

- Analysis of mitigation effectiveness, costs and implementation. chemical protectants and mitigation behavior, in terms of developing and producing resistent crop varieties, may potentially reduce ozone induced crop yield losses at low cost. Additional studies on the costs and effectiveness of these actions are merited to reduce the burden of ozone impacts and ozone control.

- Improved economic assessment. The NCLAN program, and other work at EPA's Office of Air Quality Planning and Standards (OAQPS) and the California Air Resources Board (CARB), have significantly increased the reliability of national and regional economic assessments. However, the models are still sensitive to many key inputs and assumptions which can be readily addressed. Model refinements important to pursue include:

  - Adding more crops, especially regional crops.
  - Sensitivity of results to omitted crops assumptions.
  - Rerunning dose-response and economic model with improved rural ozone data.
  - Additional model development to deal with government subsidy issues, international trade, sensitivity analysis on economic inputs and assumptions on demand elasticities, substitution activities, etc.
  - Expansion of the issue of what is an "adverse" impact.

- Urban ornamentals. Urban ornamentals are exposed to significant ozone levels and may be associated with significant welfare loss. Initial assessments of damage magnitudes are warranted for grasses, bushes, and trees. If damages are potentially large, then longer-term research should be planned.

Third Priority Research Needs

- Genetic control of pollutant susceptibility. NCLAN and other research efforts have generally addressed ozone impacts with the most intensively-used cultivars of key crops. Breeding for improved yield and harvesting characteristics continually produces new cultivars with unknown pollutant susceptibility. Better understanding of how susceptibility to injury and yield reduction by exposure to ozone is inherited would enable the inclusion of pollutant susceptibility in the list of desirable characteristics used in breeding new crop cultivars.

2. Forests

a) Objectives

Currently, there is a substantial research program supported by EPA, the U.S. Forest Service (USFS), the Electric Power Research Institute (EPRI), and the National Council on Air and Stream Improvement (NCASI)

concerning tree response to acid rain and related pollutants including ozone. This program is coordinated under the National Acid Precipitation Assessment Program (NAPAP), which is required to provide an overall assessment by the year 1990.

Current short-term research efforts of NAPAP will provide a basis for a first-order evaluation of tree response to pollutants. Given the perennial nature and longevity of trees, their close association with climatic factors, and the likelihood that emissions of precursors of ozone and acid rain will continue into the next century, we recommend that EPA focus upon developing a long-term program of research on forest response to pollutants, including ozone.

The aim of the EPA long-term program should be to extend the initial efforts of NAPAP and provide a more thorough and extensive evaluation than can be obtained from a short-term research program. The EPA research plan should provide for interim changes in emphasis because the assessment to be completed in 1990 will undoubtedly provide important guidelines for future research. The plan should provide for a coordinated program of research on effects of ozone and other long-range transported pollutants on forests to insure continuity of effort over a period of at least ten years.

b) Research Needs

The needs specifically identified in this section are long-term research directives.

First Priority Research Needs

- Exposure statistics. Given the perennial habit of trees and their close dependence on edaphic and climatic conditions, quite different exposure statistics may be required to protect forests against injurious effects of ozone and other pollutants. This work will take a long time period to resolve because it must take into account cumulative effects and the capacity of trees to recover from stress.

- Ozone dose-response of major tree species and overall forest productivity analyses. Dose-response relationships between ozone and other long-range transported pollutants and trees need to be developed using field chambers on whole trees and/or on branches of mature trees. These, too, will have to be long-term studies because the effects of competition, and different edaphic and climatic conditions on growth, development, competition, and reproductive success need to be established. These long-term studies also need to address the effects of air pollution impacts on trees upon the entire forest ecosystem in a unified approach.

- Generalizable tree physiological models. Physiological models have greatest potential for prediction of effects over long time periods. To be of greatest value, they should be linked to models of climate change and geochemical cycling of elements. Model development is a difficult undertaking and requires a substantial multidisciplinary effort. Therefore, this research requires secure funding over a substantial period of time.

Second Priority Research Needs

- Economic model development. This includes considerations of forest productivity and succession, aesthetics and non-timber service flows from forest ecosystems. In the long-term, this analysis requires a comprehensive and integrated forest ecosystem valuation framework. Work should also extend and integrate available regional timber models, account for different timber quality and design sensitivity analyses of the economic models. This research must be closely linked to the other research efforts because it is dependent on them for accurate inputs.

c) Short-Term Research Initiatives

While the most important focus should be upon long-term initiatives, several short-term initiatives already underway or planned that CASAC supports. These include, but are not limited to:

- Characterization of the resource at risk. Mapping of forest resources against ozone levels and current information/hypotheses about tree species sensitivity to assess the resource at risk are used as a tool that can be updated and improved as the science developes. These efforts are underway at EPA, the California Air Resources Board, the National Park Service and elsewhere.

- Retrospective study. A resurvey of the San Bernardino National Forest to validate projected impacts, trace long-term tree impacts and succession, validate or reject hypotheses and review other forest ecosystem impacts would provide substantial insight in developing long term direction.

- Preliminary economic studies. These studies are underway under the NAPAP program and will provide useful information upon which to develop long-term analyses.

IV. RESEARCH NEEDED FOR FUTURE DECISIONS ON NATIONAL AMBIENT AIR QUALITY STANDARDS FOR LEAD

A. Introduction

Since 1977 there has occurred a steady downward trend in atmospheric lead concentrations along with a similar downward trend in the lead burden of adults and children. Although both of these trends are impressive, concerns about the impact of lead on human health remain a valid scientific and public policy issue. This is mainly because of recent epidemiological evidence that adverse effects occur at levels of exposure previously thought to be safe. In short, lead exposure is declining while perceptions and evidence of what constitutes a safe level of exposure are also shifting downward. The implications of this development for future directions of research are substantial. For exposure issues, the current major contributions to total lead intake are quite different than previous data indicated, at least as applies to the general population. Since scientists and regulators have indentified biomedically adverse effects within the usual range of human exposure, EPA needs better information on which media and sources to target for further reduction in human exposure.

Further lead exposure reduction may not prove to be equally feasible or sufficient to prevent harm to certain populations at risk, notably the fetus. Information, therefore, is needed concerning the circumstances (apart from high lead exposure) which result in adverse effects in certain individuals but not in others, e.g. unusual patterns of lead absorption and deposition.

The Committee discusses these and other issues in approximate order of their urgency and importance, bearing in mind the regulatory role of EPA. It strives to make research recommendations to better inform the Agency's decisions on whether to take further regulatory actions to minimize the risk of adverse health effects due to lead.

Finally, EPA staff requested the Committee to present recommendations concerning the design of the forthcoming National Health and Nutrition Evaluation Survey (NHANES III). The earlier NHANES II survey, completed in 1980, proved to be a valuable resource for identifying health effects of lead in the general population that were not widely understood at that time. In developing its recommendations, CASAC recognizes that any broad-based survey e.g. NHANES, has competing scientific needs and priorities to reconcile. The Committee has relied heavily upon the OAQPS staff paper and the EPA Air Quality Criteria Document for Lead as source documents for this activity.

B. Atmospheric Processes

The phasedown in the sale of leaded gasoline has probably been the major contributor to the accompanying reduction in ambient air levels of lead. The specific extent to which this is true has some remaining uncertainties since other regulatory actions have been in effect during the same general time period. Basically, this has been a matter of enforcing regulations which limit the emission of lead from point sources to achieve and maintain ambient air quality levels at or below 1.5 ug lead/m^3. The Committee urges EPA to reassess the relative impact of various point sources and of leaded gasoline on general ambient air lead concentrations. As one means of implementing this recommendation, EPA should consider the use of existing, or the development of new, tracer techniques.

EPA's regulation of ambient lead has exclusively focused on inorganic lead, although it is known that alkyl species of lead exist in the environment. Alkyl lead is released from sources such as the use of tetra-ethyl lead (TEL) in mobile sources. Inorganic lead can be alkylated in the environment. Little is known of the distribution of alkyl lead, its concentrations in ambient air, or the processes of bioalkylation. Because of the substantial toxicity of alkyl lead compounds, additional research on these topics is useful.

Sampling sites should include areas in the immediate vicinity of major stationary sources such as primary and secondary lead smelters, battery plants, and other sources such as municipal waste incinerators. Such sites should be distributed around the country to capture different climatic and geographic conditions.

The above recommendations have high priority, but the impact of lead emissions on total lead concentrations in various media is an equally important issue. Current estimates relating air lead concentrations to surface soil and dust lead levels are derived mostly from older studies with no site-specific indication of whether the trends are upward or downward. A series of measurements are needed, over time, in various locations to assess the impact of changes in lead air quality and particle size on soil and dust lead pools and other sources (e.g., snow) of deposited lead accessible to children, and the turnover rate of lead in these media. Sites selected for study should include areas where the total lead concentration is both high and low. This is necessary in order to identify the role of atmospheric contributions and compare it with other pathways.

Because of their relevance to deposition processes, more attention should be given to the measurement and characterization of lead particle size distributions. It is also important to determine the chemical compostion of both the lead-bearing particulates and the chemical form of the lead in the matrices. Such investigations would provide a basis for

tracing the source(s) of lead in the air using fingerprinting techniques and would assist biologists researching the bioavailability of lead as it relates to chemical composition.

EPA already is confronted with the need to make decisions concerning the disposal of lead-contaminated soil and refuse. There is a pressing need for more information about the transfer of lead to the general environment from dump sites via ground water and air. Such information would greatly aid in establishing criteria for identifying those dump sites having minimal input on human exposure to lead.

First Priority Research Needs

The following recommendations are assigned approximately equal, first priority. To the extent that is necessary to implement these recommendations, EPA should consider developing new tracer methodologies.

- Reassessment of the relative impact of point sources and gasoline on ambient air lead.
- Assessment of the impact of air lead on lead in various media to which man is exposed, with special emphasis on food and water.
- Assessment of factors which determine the transfer of lead from dump sites to air and water.

Second Priority Research Need

- Studies concerning the concentration, speciation and sources of alkyl lead in ambient air.

C. Exposure Considerations

It is especially important to quantify the amount of dust and soil that young children ingest through hand-to-mouth activities in various settings and to examine in detail the factors that influence lead exposure through this route (e.g., household dust lead levels, parental occupations, housekeeping practices, thumb-sucking, finger licking and nail biting tendencies, and child-rearing practices.)

Bioavailability of ingested lead (and of inhaled lead) is another issue urgently in need of intensive investigation. Estimates of the impact of soil lead concentrations on the blood lead of young children have varied widely from one study to another. Essentially nothing is known, however, about the reasons for these discrepancies. In the absence

of more specific information it is difficult, if not impossible, to make rational site-specific decisions as to maximum safe limits of lead in soil or dust. The influence of chemical and physical characteristics of lead in soil and dust on bioavailability, therefore, needs to be thoroughly investigated.

Given the growing data base identifying lead-contaminated soil, and both interior and outdoor dust, as major remaining exposure sources for children (especially in older urban areas), it is increasingly important to determine the most effective soil-lead abatement protocols. These abatement protocols should include evaluation of removal of lead-based paint and lead-contaminated street and house dusts, as well as lead-contaminated soil.

Although a great deal of information is available concerning human exposure to lead from multiple sources, much of it may no longer be valid, particularly if gathered a decade ago or more. Changing technology (e.g. food packaging), eating habits, and reduction of lead emissions may have substantially altered the relative importance of the various sources, as well as the level of total intake. A reassessment of exposure needs to be undertaken in order to properly identify the most promising strategies aimed at further reduction in human exposure.

Because harmful effects from lead exposure have been observed at relatively low levels, particularly to the fetus, the relative contributions of various sources, under normal conditions of intake must not be overlooked, EPA should work with the Food and Drug Administration to evaluate the means by which lead significantly enters the classes of foods which contribute most to total dietary intake, beginning with the raw products and ending with the fully processed and packaged products.

Studies are also needed to determine how much lead derived from tap water is consumed by various segments of the population (e.g. children and pregnant women). This effort should take into account the use of water for food and beverage preparation, in addition to water which has remained overnight in plumbing. Such water contains considerably more lead than water drawn after the plumbing has been flushed.

In connection with the forthcoming NHANES III study the CASAC urges EPA to consider questionnaire items to aid in establishing whether the subject's blood lead concentration is representative of a fairly constant long-term exposure history or whether some recent significant change in exposure is to be considered in interpretation of the data, e.g. recent interior renovation of an old residence which had been grossly contaminated with lead-base paint. Second, NHANES planners should consider the importance of using the best possible methodology for blood lead determinations, given the low concentrations and relatively narrow range which will likely be encountered.

First Priority Research Needs

All of these are assigned first priority, although EPA's responsibility is uncertain in some cases.

- Determination of the importance of soil and dust ingestion as sources of lead exposure in young children, taking into account social and other factors that influence such ingestion.

- Bioavailability of lead, particularly in soils and dusts as a function of particle sizes and chemical form.

- Reassessment of the contribution of foods to total lead intake, including the contributions attributable to food processing and packaging.

- More detailed determination of the contribution of drinking water to total lead intake, including water used in food and beverage preparation.

D) Lead Metabolism

Past studies of the relationships between dose and effects of lead in man have relied almost exclusively on whole blood lead as the index of dose. Scientists now recognize that this index has shortcomings. It reflects only recent exposure, and it does not bear a linear relationship to concentrations in tissues or at receptors, e.g. ALAD. Thus, development of better biomarkers of human lead exposure and techniques for measuring lead concentrations in biological media are needed. X-ray fluorescence instrumentation for in vivo measurement of lead in mineralized tissue appears promising and ought to be further explored. This should include investigations of novel biomarkers of dose. As an example, kidney and brain tissue contain a unique lead-binding protein which may be of diagnostic interest to assess toxic manifestations of lead exposure. Development of a radioimmunoassay for detection of this protein in biological fluid specimens such as urine is underway. This is particularly important since current biomarkers are either inadequately sensitive (e.g. erythrocytic protoporphyrin) or are not readily amenable to field investigations (e.g. ALAD).

There is also a need to develop better methods for monitoring fetal lead exposure across the full period of gestation. This is a challenging problem requiring some innovative ideas and the use of more appropriate animal models of human pregnancy than rodent species e.g. perhaps sheep and subhuman primates.

Better understanding also is needed of the impact of bone resorption in old age on the concentration of lead in blood and, more importantly, at lead-sensitive sites. Thus, biokinetic modeling of lead metabolism

must include detailed attention to the significance of bone stores of lead, particularly in situations where calcium mobilization occurs, i.e. pregnancy, lactation and old age.

The question of how various dietary constituents affect lead absorption and tissue distribution in man is very poorly understood, not only in the general population, but in special risk-associated groups (e.g., children; pregnant, lactating, or postmenopausal women). Specifically, the effects of varying levels of calcium, iron and, perhaps, of high sulfur in the diet may be of particular relevance.

First Priority Research Needs

- Development of better indices of lead exposure, notably lead in hard tissues and circulating lead-binding proteins.
- Biokinetic modeling with special emphasis on the fetus and placenta, as well as bone in both pregnant women and in the elderly.
- Dietary factors influencing lead absorption.

E. Biological and Health Effects

1. Developmental Effects

Recent epidemiological evidence reinforces and extends the conclusion that the early stage of human development is an especially critical period for deleterious effects of low-level lead exposure. Findings from prospective studies in Boston, Cincinnati, Port Pirie (Australia), and Cleveland indicate that disturbances in fetal development, as well as postnatal neurobehavioral development, may occur at lead exposure levels well below those previously considered "safe" or even "normal". The most clearly identified effect thus far has been lower scores on the Mental Development Index of the Bayley Scales of Infant Development, a well-standardized test of infant intelligence. Other developmental endpoints such as shorter gestational age and lower birth weight have also been associated with prenatal lead exposure in many of these studies.

Results of these studies to date suggest that adverse effects resulting from prenatal exposure may be largely irreversible, at least within the first 2 years of life. Ongoing prospective studies, therefore, should be continued without interruption, at least to the age at which school performance can be properly evaluated, and even on to puberty.

Additional prospective studies of the effects of lead on pregnancy outcomes also are needed, focusing on such unresolved issues as whether fetal exposures at maternal blood lead concentrations higher than in current studies result in correspondingly greater adverse cognitive outcomes, or whether different (or additional) adverse effects emerge. Although of considerable interest, such studies would be of lesser importance than additional studies at current general lead exposure levels, examining the impact of lead exposure when combined with other factors known to carry a risk for adverse fetal outcomes, e.g. diabetes.

Because so little is known regarding the mechanism whereby lead acts to compromise fetal development, the Committee is uncertain as to what specific measurements should be recommended for inclusion in NHANES III that would add to current knowledge regarding the effects of lead on pregnancy outcome. It urges that those designing the study consult with qualified reproductive endocrinologists and reproductive toxicologists to develop recommendations concerning possible neuroendocrine measurements that would be useful in assessing adverse influences on fetal development. Also, developmental psychologists currently studying the effects of lead on postnatal neurobehavioral development should be asked to review any currently proposed battery of psychological and neurophysiological tests for the purpose of recommending additions or modifications that would enhance their utility in furthering knowledge regarding adverse effects of lead exposure.

Numerous animal studies currently in progress are aimed at gaining a better understanding of mechanisms by which lead adversely affects neurobehavior. Most of these studies focus on electrophysiological, neurochemical and behavioral endpoints. These should continue to be supported, but the Committee recommends that more emphasis be placed on neuroendocrinological influences on brain development and function, and on the reversibility of adverse effects.

There are large information gaps regarding the dose-response relationships of chronic alkyl lead exposure in the general population (particularly pregnant women and infants) using measures of subtle neurobehavioral or other effects. Although it seems unlikely that alkyl lead is harmful at the concentrations likely to occur in general ambient air, this judgment is based on occupational exposure rather than on exposure of fetuses and infants or animal models thereof. Appropriate animal studies should be undertaken to establish the relative potency of chronic alkyl lead vis a vis inorganic lead using sensitive indices of effects.

2. Cardiovascular Effects

As discussed in the recent addendum to the EPA Air Quality Criteria Document for Lead (1986), a growing body of literature suggests that low level lead exposure has both direct and indirect effects on end-arteriolar

smooth muscle contractility and cardiac function, and thus essential hypertension may be causally related to chronic low-level lead exposure, though this is far from certain given the small effect reported (approximately 2-7 mm Hg per 15 ug Pb/dl in blood). Nonetheless, a better understanding of the health implications of lead effects on the cardiovascular system is needed since a large number of people are potentially at risk. Prospective human studies would be desirable in principle, but the power of such studies would need to be carefully evaluated. Although a study of the morbidity and mortality implications of the hypertensive effects of lead also would be desirable, the feasibility of obtaining useful studies is questionable.

Studies in experimental animals and studies conducted in occupational exposed workers strongly suggest that the blood pressure effect occurs only within a rather narrow range and that, in fact, lead may have a hypotensive effect at exposure levels somewhat above the range in the general population. It is, therefore, important that future epidemiological studies should be designed to include a wide range of lead exposures. Future animal studies should be directed toward gaining a better understanding of the mechanism(s) underlying the hypertensive effect of lead, particularly in regard to the effects of lead on the second messenger functions of calcium.

The Committee is pleased to note that the forthcoming NHANES III study will include a determination of cadmium concentrations along with lead since the vasopressor effects of lead and cadmium may be additive. It is the Committee's impression, however, that blood cadmium has never been shown to correlate well with toxic effects. Perhaps cadmium metallothionein (CdMt) in serum would be better than elemental Cd concentrations as a biomarker. It is our understanding that a sensitive radioimmunoassay for CdMt has been developed. Cadmium experts should be consulted.

3. Other Effects

The two most currently significant health effect issues are those relating to growth and development in children, and to hypertension in adults. These appear to be critical effects, using the term "critical" to denote "most lead-sensitive". If this belief is correct, further reductions in lead exposure should serve to decrease the risk of other adverse effects to which man may be less or equally sensitive. More information is needed regarding the significance of other effects, particularly in subpopulations other than those already identified as being most sensitive to neurobehavioral and cardiovascular effects. As an example, old people are a separate subgroup peculiarly sensitive to factors which contribute to the development of osteoporosis. The impact of lead on the incidence and severity of osteoporosis needs more attention. Again, some valuable information in this regard may emerge from the NHANES III study, particularly if cadmium exposure can also be effectively assessed. Cadmium has been shown to induce bone resorption and

osteoporosis in postmenopausal women, particularly in conjunction with Vitamin D deficiency. A major contributing factor may be the fact that cadmium accumulates in the body with age to an even greater degree than lead. Further, there is evidence that lead also has toxic effects on bone development. Admittedly, the evidence is very limited and has focussed mainly on young children and young experimental animals. Possible additive effects involving lead and cadmium should be investigated. This should include studies of the toxicokinetics of skeletal lead, including the influence of age (See discussion under Lead Metabolism). In this context, NHANES III should consider including a sufficient number of old people to establish whether a significant lead problem exists. A meaningful measure of vitamin D status is also important, serum 1,25 dihydroxycholecalciferol in particular.

Numerous studies have reported effects of lead on the immune system, and a small number of studies report an association between lead and cancer. No convincing evidence has surfaced, however, suggesting that lead is a human carcinogen or that it has any role in the etiology of other diseases involving the immune system. EPA should consider convening a small group of immunotoxicologists and experts in oncogenic toxicology to jointly examine whether current information identifies any particular sub-population in which a special risk may exist involving the effects of lead on the immunological system and the sometimes-related cancer endpoint.

Although the scientific literature identifies other potential toxic effects of lead, there is no current basis for believing that current standards do not adequately protect against known or potential effects.

First Priority Research Need

The Committee recommends the following issue as a first priority research need:

- Continued, uninterrupted support for current prospective studies of neurobehavioral effects of lead in children to school age and beyond.

Second Priority Research Needs

Other recommendations are made as only somewhat lesser second priority research needs:

- Additional prospective studies examining fetal and early postnatal development examining a wider range of fetal lead exposures, and with additional risk factors, e.g. diabetes and toxic substances other than lead.

- Continued support for investigations concerning the mechanisms whereby lead adversely affects neurobehavior with greater emphasis on neuroendocrinological influences on brain development.

- Initiation of prospective studies of the relationship of the lead exposure to blood pressure, as well as consideration of the consequences with respect to the incidence of hypertension. Although this is an important objective, the subcommittee recognizes that it may not be feasible.

- Initiation of studies regarding the role of lead exposure in osteoporosis. This should include epidemiological approaches and investigation of mechansims using animal models.

- Studies of toxic effects of alkyl lead compounds most prevalent in the environment, with emphasis on subtle chronic effects in developing animal systems and potency relatie to inorganic lead.

Finally, the Committee recommends (with moderate enthusiasm) that the EPA convene a meeting of immunotoxicologists and oncogenic toxicologists to assess further research needs relating to the possible role of lead in cancer and other diseases involving the immune system.